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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,534	01/25/2002	Harry R. Davis	CV01378K	2339

24265 7590 03/24/2005

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
WANG, SHENGJUN	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,534	DAVIS ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *4,29,30,37-69,73,78 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-28,31-36,70-72,74-77,79,80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Receipt of applicants' remarks submitted January 10, 2005 is acknowledged.

Claim Rejections 35 U.S.C. 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3, 5-28, 31-36,70-72, 74-77 and 79-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenblum et al. (US 5,846,966, IDS) in view of Albright (US 5,300,288), Dechow (US 4,837,255), and Davis (US 5,661,145, IDS).

1. Rosenblum teaches the instant cholesterol absorption inhibitors and its application for lowering serum cholesterol. Rosenblum further teaches that the cholesterol absorption inhibitors may be employ in combination with other cholesterol lowering agents, such as simvastatin. See, particularly, the abstract, and the claims. Rosenblum et al. teach that daily dosage of the compounds is about 5mg to 1000 mg, given in a single dose or 2-4 divided doses. When used in combination with other drug the dose is about 1mg to 1000 mg a dose given 1 or 2 times a day. The exact dose would depend on various conditions. See, particularly, col. 21, lines 17-63.

3. Rosenblum et al. does not teach expressly a combination of a hydroxy-substituted azetidinone compounds, e.g., ezetimibe, and a bile acid sequestrant, e.g., cholestyramine, or further with a cholesterol biosynthesis inhibitor, e.g., simvastatin.

4. However, as shown in Albright, cholestyramine is an old and well-known cholesterol-lowering agent. See, column 2, lines 3-7. Dechow particularly, teaches a method of lowering

cholesterol by administering to a patient a composition comprising cholestyramine. See, particularly, the claims. Davis teaches that simvastatin is a known cholesterol biosynthesis inhibitor, and is particularly useful with lactam cholesterol absorption inhibitor. See, particularly, column 2, lines 51-63.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make cholesterol lowering composition comprising the hydroxy-substituted azetidinone compound, ezetimibe, and the well-known cholesterol lowering agent, cholestyramine.

A person of ordinary skill in the art would have been motivated to make cholesterol lowering composition comprising the hydroxy-substituted azetidinone compound, ezetimibe, and the well-known cholesterol lowering agent, cholestyramine. It is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known cholesterol lowering agent sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. The further employment of simvastatin in the combination is obvious because the hydroxy-substituted azetidinone compounds are known to be useful with cholesterol biosynthesis inhibitor. Further, the optimization of a result effective parameter, e.g., effective amount of a therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215.

As to the specific amount of ezetimibe, note the amount (10 mg) is within the range disclosed by Rosenblum et al. In the case where the claimed ranges "overlap or lie inside ranges

disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Further, Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Response to the Arguments

Applicants' remarks submitted January 10, 2005 have been fully considered, but are not persuasive.

5. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The rejections set forth above do not use any knowledge that is not available to one of ordinary skill in the art at the time the claimed invention was made.

6. Applicants further argue that In re Kerkoven was misused in the rejections because the ingredients in the claimed combination function through different biochemical mechanisms. The arguments are unpersuasive. Even though the detailed biological functions of those ingredients

may be different, the ultimate results are the same, i.e., lowering the level of cholesterol. Therefore, ingredients herein have been known to one of ordinary skill in ten art as therapeutical agents used for the very same purpose, i.e., lowering the level of cholesterol. Further, the cited references have suggested the use of different cholesterol lowering agents together.

Applicants' arguments fail to reach the instant rejections core issue; that concomitantly employing compounds, old and well known for the same use is obvious to the skilled artisan. To overcome this rejection Applicants must illustrate the presence of unexpected benefits in the resulting mixture. Any combination not shown to possesses such unexpected benefits must remain properly rejected as obvious. In illustrating unexpected therapeutic benefits the Applicant must test all active components individually to ensure a greater than additive therapeutic benefit. A prima facie case of obviousness has been established. There is no objective evidence supporting an unobviousness of claimed invention.

For reasons discussed above, the claims have been properly rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER

Shengjun Wang
Primary Examiner
Art Unit 1617